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September 11, 1997

Ms. Amanda Bryce Norton
Chief Mediator and Ombudsman
Office of the Commissioner
Room 14-105, HF-7
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BY HAND DELIVERY

Re: Periostat® NDA 50-774; Request for Designation

Dear Ms. Bryce Norton:

This request is submitted on behalf of our client, CollaGenex Pharmaceuticals, Inc. ("CollaGenex" or the "Company"). We hereby respectfully ask that the Food and Drug Administration ("FDA" or the "agency") designate the above referenced drug, which is the subject of a pending new drug application ("NDA"), as subject to the provisions of section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 355(b).

While we recognize this is not a typical designation request that is submitted under 21 C.F.R. Part 3, it nonetheless involves a significant product jurisdictional question appropriate for resolution by the Ombudsman's office. The precise issue addressed herein is whether Periostat® is properly subject to the antibiotic provisions of section 507 of the FDC Act, 21 U.S.C. § 357. In this regard, Periostat® does not meet the statutory definition of an "antibiotic drug." It is a synthetic drug that is neither intended for use as an antimicrobial drug product nor is it capable of inhibiting or destroying microorganisms at the dose levels that are utilized for periodontal disease. Therefore, Periostat® should not be subject to the antibiotic provisions of section 507 of the FDC Act.

Further in connection with this designation request, we respectfully request a waiver of 21 C.F.R. § 3.10, assuming the applicability of 21 C.F.R. Part 3 to this request. This provision provides that the application review clock is stayed during the pendancy of review by the product jurisdiction officer. Since this request does not pertain to which center(s) within FDA should have primary jurisdiction, but rather to which section of the FDC Act is pertinent to the approval of Periostat®, no reasons exist to stay the review of the pending NDA for Periostat® because of the submission of this designation request. Any decision in response to this petition will not affect jurisdiction of the Center for Drug Evaluation and Research ("CDER"), which is responsible for review of the NDA for Periostat®. We assume therefore that the waiver request has been granted upon the acceptance for filing of this designation request by FDA, unless we hear otherwise. Note that if this request is not granted upon acceptance of this petition for filing, then you should consider this submission withdrawn.

In accordance with 21 C.F.R. § 3.7, the following information is submitted:

IDENTITY OF SPONSOR

CollaGenex Pharmaceuticals, Inc.
301 S. State Street
Newton, PA 18940

Establishment Registration Number:	Not applicable.
Company Contact Person:	Mr. Christopher V. Powala Director, Drug Development & Regulatory Affairs
Telephone No.:	215-579-7388, extension 16
Facsimile No.:	215-579-8577

PRODUCT DESCRIPTION

Classification Name:

Not applicable.

Common, Generic, or Usual Name:

Doxycycline hyclate capsules USP (20 mg.)

Proprietary Name:

Periostat®.

Chemical, Physical, or Biological Composition:

Each Periostat® capsule is formulated to contain 20 mg of doxycycline hyclate USP as the only active ingredient.

Status and Brief Reports of Development Work:

With respect to the indicated use of doxycycline that is the subject of this request, in 1983, it was demonstrated that a semisynthetic tetracycline, minocycline, could inhibit collagen breakdown in the uncontrolled diabetic germ-free rat model of periodontal disease by a mechanism independent of its antimicrobial properties (Vol. 2.2. pp. 21-26). Further studies illustrated that this effect was achieved by blocking host-derived matrix metalloproteinases ("MMPs") (collagenase) and thus inhibiting bone and collagen loss. Animal studies have demonstrated that the tetracyclines, which have been chemically altered to render the molecule to be devoid of any anti-microbial activity, also

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Since it is impossible to include copies of all of the referenced information without exceeding the page limitations specified at 21 C.F.R. § 3.7(c), we are providing instead general citations to relevant volumes of the NDA 50-744 for Periostat®.

inhibit other matrix metalloproteinases, such as gelatinase and macrophage elastase, and thus can inhibit connective tissue destruction by a non-antimicrobial mechanism (Vol. 2.5, pp. 4-155). It also was found that doxycycline was the most potent inhibitor of MMPs of all the commercially available tetracyclines.

It has been shown in clinical studies that collagenase activity was reduced in gingival crevicular fluid as well as in adjacent gingival tissue after 14 days of 20 mg b.i.d. doxycycline hyclate administration (Vol. 2.109, pp. 1-8; 91-101). During a 12-week study evaluating the effects of doxycycline hyclate, 20 mg b.i.d. and placebo in patients with adult periodontitis, it was demonstrated that:

- No significant changes in gingival inflammation occurred, but there was a significant reduction of gingival crevicular fluid flow, an indication of MMP activity;
- Clinical parameters of tissue breakdown, *i.e.*, clinical attachment level and pocket depth, were significantly improved;
- Gingival crevicular fluid collagenase activity was statistically significantly reduced by 47.3 percent;

Description of Manufacturing Process:

CollaGenex relies on third-party contract manufacturers to produce doxycycline hyclate, the active ingredient in Periostat®, and to manufacture the finished dosage form (Vol. 1.1, CMC Section).

Proposed Use or Indications:

Periostat® is intended for use as a part of a professional oral health program to promote periodontal attachment gain and to reduce bone loss, pocket depth and bleeding on probing in patients with adult periodontal disease (Vol. 202, pp. 1-17).

Description of Modes of Action:

MMPs are an important family of zinc- and calcium-dependent endopeptidases secreted or released by a variety of host cells (*e.g.*, polymorphonucleocytes, macrophages, bone cells, and fibroblasts) that function at neutral pH and use the various constituents of the extracellular matrix as their substrates. These proteinases are involved in normal physiologic events such as bone remodeling and involution of the post-partum uterus. A variety of pathologic processes are characterized by elevated levels of MMPs, however, giving rise to increased connective tissue breakdown. These disease processes include rheumatoid and osteoarthritis, osteoporosis, and cancer metastasis. In particular, it has been shown that adult periodontitis is accompanied by increased levels of neutrophil collagenase in the gingival crevicular fluid.

Unlike existing treatments which focus on the bacterial infection associated with periodontitis, Periostat®, as a MMP inhibitor, disrupts the chronic progressive tissue degradation characteristic of the disease. As discussed in the Periostat® NDA (Vol. 2.2, pp. 21-26), the active ingredient in Periostat® (doxycycline hyclate) treats periodontitis by inhibiting matrix metalloproteinases (*i.e.*, leukocyte-type and fibroblast-type collagenase, gelatinase, and macrophage elastase) (Vol. 2.5, pp. 4-155). This mechanism of action is independent of the drug's antimicrobial properties at higher dosage levels (Vol. 2.18, pp. 1-50).

As also discussed in the Periostat® NDA, doses below 50 mg q.d. doxycycline hyclate are not effective in providing a measurable antibacterial effect (Vol. 2.18, pp. 1-50). The data and information submitted in support of the Periostat® NDA confirm that doxycycline hyclate at doses of 20 mg. q.d. or 20 mg b.i.d. provide a serum doxycycline concentration below the minimum 1.0 µg/mL doxycycline concentration (Vol. 2.2, p. 77). The results show that plasma concentrations were at a steady state by day 7 for the three treatment groups, with the mean pre-dose plasma doxycycline concentrations at steady state ranging from 0.13 to 0.14 µg/mL, 0.32 to 0.34 µg/mL, and 0.25 to 0.31 µg/mL following 20 mg q.d., 20 mg b.i.d., and 50 mg q.d. dosing, respectively. The mean steady state concentration and the mean steady state maximum concentration values following doxycycline hyclate treatments of 20 mg q.d. and

20 mg b.i.d. were all statistically significantly lower than 1.0µg/mL, the accepted threshold for antimicrobial activity.

Also, in terms of this request, nonclinical studies cited in the Periostat® NDA using culture plate analysis and speciation via DNA probe analysis showed no anti-bacterial effect of doxycycline hyclate 20 q.d. or 20 mg b.i.d. (Vol. 2.18, pp. 1-50 and Vol. 2.19, Report 5732.11F). No effects were observed on total anaerobic bacteria *Actinobacillus actinomycetemcomitans, Prevotella intermedia,* or *Porphyromonas gingivalis, Fusobacteria,* or *Actinomyces* from the periodontium of patients with adult periodontitis.

Recent studies have shown that doxycycline and novel tetracycline analogs chemically modified to render them devoid of antimicrobial activity can inhibit connective tissue breakdown by a variety of direct and indirect mechanisms including (Vol. 2.5, p. 4; Vol. 2.2, pp. 21-26):

1. Direct, non-competitive inhibition of active collagenase, which appears to depend on the Ca++ and Zn++ binding properties of doxycycline;

2. Prevention of the conversion of pro-collagenase to collagenase, which appears to be independent of metal ion binding properties; and

3. Inhibition of the degradation of the serum protein, α_1-proteinase inhibitor.

Alpha$_1$-proteinase inhibitor is involved in the inhibition of other tissue destructive enzymes such as elastase which are not directly inhibited by doxycycline. Maintenance of high concentrations of α_1-proteinase inhibitor in tissue would protect elastase-susceptible connective tissue components such as elastic fibers, fibronectin, and proteoglycans, as well as maintaining high levels of the naturally occurring TIMPs (tissue inhibitors of metalloproteinases), which are also substrates for elastase.

Schedule and Duration of Use:

Periostat® is recommended for long-term daily use (up to one year) at dose level of 20 mg b.i.d.

Dose and Route of Administration:

Periostat® is intended solely for oral administration.

Description of Related Products and Regulatory Status:

Existing therapies and those treatments known by the Company to be under development for periodontitis are designed primarily to treat the bacterial infection associated with periodontitis on a short-term, periodic basis. These treatments include mechanical and surgical techniques, prophylactic approaches, such as mouthwashes, and locally delivered therapies.

We note that a variety of drugs indicated for antimicrobial use are sometimes regulated under section 507 of the FDC Act and sometimes not. These include metronidazole, which is subject to section 505. The precise basis for why some anti-infectives are classified as antibiotics and others are not is unclear. The agency appears to have been inconsistent in defining drugs that are subject to section 507.

Other Relevant Information:

By way of background, CollaGenex submitted to FDA the referenced pending NDA for Periostat® on August 30, 1996. The Periostat® NDA was accepted for filing on October 29, 1996. When CollaGenex originally submitted the application it was designated as NDA No. 20-642. On September 16, 1996, however, CDER's Division of Dermatologic and Dental Drug Products (the "Division") informed the Company that the NDA number had been changed to 50-744, a reflection of the fact that FDA assigns the 50,000-series numbers to full antibiotic applications. Nonetheless, the application is currently being reviewed by the Division of Dermatologic and Dental Drug Products, not the

Division of Anti-Infective Drug Products. Various FDA personnel have informed CollaGenex that its application is being handled and reviewed under section 507 of the FDC Act.

The Dental Drug Division advised CollaGenex when it filed the NDA that CollaGenex could request that the NDA be designated as a 505(b) application. The Company was also informed, however, that the submission of such a request at that time could significantly impede the agency's acceptance of the NDA for filing and substantive review. The Division also suggested that CollaGenex revise the applicable NDA cover letter and readdress the new drug/antibiotic designation issue once the NDA had been accepted for filing. Therefore, on September 17, 1996, CollaGenex submitted a revised cover letter and Form FDA 345h to reflect the new NDA number and to state that the NDA was submitted pursuant to section 507 of the FDC Act rather than section 505.[1] The Company is now addressing the antibiotic issue that is in dispute by the submission of this designation request. Although the agency component (CDER) is not in question, the product jurisdiction of Periostat® under section 507 is in dispute.

CollaGenex's Recommendation:

CollaGenex agrees that the agency component with primary jurisdiction for the review of the Periostat® NDA should be the Center for Drug Evaluation and Research, particularly the Division of Dermatologic and Dental Products, not the Division of Anti-Infective Drug Products. Given the mechanism of action of and the indicated use for the drug which is the subject of NDA 50-774, the Anti-Infective Division would not be the appropriate Division to review the subject NDA. CollaGenex also believes that the appropriate classification of its product is as a non-antibiotic drug subject to approval under section 505, not section 507, of the FDC Act, for the reasons discussed below.

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[1] Certain written correspondence that CollaGenex received from FDA regarding NDA 50-77 subsequent to that date states that the application was submitted pursuant to section 505(b) of the FDC Act. An action letter received on August 27, 1997, however, states that the NDA is not approvable under section 507 of the Act.

The relevant provisions pertaining to this recommendation are sections 201(g) and 507(a) of the FDC Act, 21 U.S.C. §§ 355(g) and 357(a). Section 201(g) is pertinent because although section 507(a) defines an antibiotic, it does so in the context of the use of the word "drug." Section 507 refers to "any drug . . . for use by man" that has certain characteristics further defined by section 507(a). Section 507 therefore cannot be read in isolation. It must be read in conjunction with section 201(g), which defines the term "drug" that is referenced in section 507.

In pertinent part, section 201(g) of the FDC Act defines the word "drug" to mean an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease of man or other animals" (emphasis added). Therefore, whether a substance is a "drug" or "drug product" subject to section 507(a) depends on the product's intended use. FDA's regulations state that the words "intended use" or words of similar import refer to the objective intent of the manufacturer or other person legally responsible for the labeling of the product. 21 C.F.R. § 201.128 (1998). Objective intent can be shown by, among other things, labeling claims, advertising materials, or oral or written statements of such persons or their representatives. *Id.*

A product subcategory which meets the statutory definition of a "drug" in section 201(g) is an "antibiotic drug" if it also meets the requirements of section 507(a). Under the FDC Act all antibiotics described in section 507 are drugs if they meet the requirements of section 201(g), but not all drugs are antibiotics. The importance of this distinction traditionally is that antibiotics can be subject to certification and other requirements, whereas most other drugs are not. More relevant today is the consideration that although antibiotics are subject to abbreviated applications,[2] they are not subject to the exclusivity provisions of Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 because they are not approved under section 505. See 57 Fed. Reg. 17950, 17951 (1992) and *Glaxo, Inc. v. Heckler*, 623 F. Supp. 69 (E.D.N.C. 1985).

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[2] See 21 C.F.R. § 314.92.

Section 507(a) of the FDC Act defines the term "antibiotic drug" to mean "any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance)" (emphases added). It is unclear what the "intended for" language in section 507 adds, if anything, beyond that same language appearing in section 201(a) pertaining to the general definition of a drug. Thus, for a product to be categorized as an "antibiotic" drug, the rest of the language in section 507 states that two requirements must be met. The drug must both be produced by a microorganism (or be the synthetic equivalent thereof) and have the "capacity" to inhibit or destroy microorganisms "in dilute solution." In short, the definition is two-pronged, stating that status of a compound as an antibiotic is dependent both on its source or, in the case of a synthetic product, on its chemical structure, and its microbial activity in "dilute solution."

Periostat® does not meet the statutory "antibiotic drug" provisions of sections 201(a) and 507(a). It neither is intended for use as an antimicrobial agent nor does it actually have the capacity to inhibit or destroy microorganisms at the recommended dosage levels that are used to treat periodontitis. The clinical and nonclinical studies described in the "Mechanism of Action" section of the Periostat® NDA, which are reflective of objective intent, clearly demonstrate that the only active ingredient in the drug product, doxycycline hyclate, is for use in the treatment of periodontitis in a manner which is not dependent upon the inhibition or destruction of microorganisms.

In terms of the "source" aspect of the first prong of the antibiotic definition, doxycycline is synthetically produced and is not obtained from microbial sources. Periostat® does not contain any quantity of a drug derived from a microbe, particularly since microbes do not produce doxycycline. Further, doxycycline is not the "chemically synthesized equivalent" of oxytetracycline. Doxycycline is chemically different from oxytetracycline. Although doxycycline is derived from oxytetracycline, which is obtained from microorganisms, this fact should not trigger the source requirement of the definition. Section 507(a) does not state that any use of a microorganism to produce a drug renders the drug an antibiotic. For example, the use of a microorganism to produce an intermediate or a precursor of a drug, including active or inactive components, should not render the product an antibiotic. If it did, this interpretation

would ignore the actual language of the statute. Moreover, such an interpretation would require the agency to engage in a thorough investigation of the source of every component used in the manufacture of a drug, perhaps even for those that do not actually appear in the final drug product.

Undue emphasis on the "source" prong of the antibiotic definition can be problematic for other reasons. In this age of modern genetic techniques, microorganisms can produce a variety of substances such as hormones, insulin, and other drugs. Then, too, biological drugs that are regulated under section 351 of the Public Health Service Act, 42 U.S.C. § 262, could also be classified as antibiotics under this prong of the definition. *See* Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (CBER), at p. 5 (excepting products of cell culture from CBER regulation that are antibiotics). Further, although antibiotic regulation was established in 1945 when there was insufficient knowledge and control of fermentation processes and methods of analysis,[3] substantial advances in manufacturing and assay methods have occurred. The current lack of any certification requirements for antibiotics is testimony to these advancements. *See* 21 C.F.R. § 433.1 (1996). Indeed, the antibiotic provisions, as originally enacted, anticipated developments that would make antibiotic certification unnecessary. *See* Statement of Watson B. Miller, May 15, 1945, on H. Rept. No. 702, 79th Cong., 1st Sess., *reprinted in* Senate Reports, 79th Cong., 1st Sess., at p. 11. For this reason, provisions were enacted in 1945 and still are contained in the law today that allow for FDA to exempt antibiotic drugs from any of the requirements of section 507. *See* section 507(c), 21 U.S.C. § 357(c).

These and other considerations discussed below indicate that whatever relative importance the "source" prong of the antibiotic definition may once have had vis-à-vis the second prong of the definition, such importance seems to have waned considerably. The substantive and distinguishing aspect of the definition in section 507(a) therefore pertains to the second prong, the capacity of a drug to inhibit or destroy microorganisms "in dilute solution." Since this quoted language is not defined in the statute or in FDA's regulations, nor does there appear to be relevant legislative

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[3] *See, e.g.*, Senate Rep. No. 1744, Views of Senators E. McKinley Dirksen and Ramon L. Hruska, *reprinted in* 1962 U.S. Code Cong. & Adm. News 2884, 2926.

history on the topic, we can only presume what may have been intended. The language seems to refer to some inherent capacity of a chemical to exert an antimicrobial effect, even when "diluted." Many chemicals can have antimicrobial effects at "high" doses, whether derived from microorganisms or not. To repeat a trite, but relevant phrase, "The dose is the poison." In the present situation, we cannot help but feel therefore that this quoted language, coupled with the intended use language of section 201(a), is a reference to the dosage level at which drugs are administered. Indeed, even classical antibiotics, such as erythromycin or penicillin, will not inhibit or destroy microorganisms to any clinically significant degree if they are sufficiently diluted. Similarly, in the "dilute solution" of the recommended dosage levels of 20 mg b.i.d., Periostat® does not have the capacity to inhibit or destroy microorganisms.

Finally, we note also that the Clinton Administration and FDA in a report entitled "Reinventing the Regulation of Drugs and Medical Devices" (April, 1995) both are committed to repealing section 507. All antibiotics would formally be made subject to regulation under section 505. Indeed, the practical reality today is that antibiotics already are regulated like other drugs subject to section 505. We therefore wish to emphasize the significant competitive anomaly posed by section 507 status for Periostat®. Without Title I exclusivity, Periostat® will be subject to generic competition immediately upon publication of a relevant antibiotic monograph. CollaGenex has invested $14 million in the development of its drug for periodontal use. An adverse decision will enable competitors to copy Periostat® and will force CollaGenex to spend millions of dollars more in defending its patents covering Periostat®. It also will likely discourage further product innovation in the anti-infective area. The potential of these additional costs could prove devastating to CollaGenex as a small company.

In light of the foregoing facts and premises considered, Periostat® is not -- and should not be treated as -- an antibiotic drug within the meaning of sections 201(a) and 507(a) of the FDC Act. CollaGenex therefore respectfully requests that FDA designate the Periostat® NDA that has been accepted for filing by the Division of Dermatologic and Dental Drug Products as subject to the new drug provisions of section 505, not section 507, of the FDC Act.

Please do not hesitate to contact me if you have any questions regarding this request for designation, if you need additional information, or if you would like to meet with us to discuss this matter further.

Cordially yours,

Edward D. Nowak

cc: Mr. Christopher V. Powala,
CollaGenex Pharmaceuticals, Inc.

Effect of Sub-Antimicrobial Dose Doxycycline on Periodontal Microbial Resistance. J. THOMAS*, C. WALKER, R. CROUT, R. METHENY, J. KARAKIOZIS, J. WETZEL, C. POWALA, and M. BRADSHAW (WVU, Morgantown, WV; UF-PDRC, Gainesville, FL; CollaGenex, Newtown, PA).

A multi-center, double-blind, placebo-controlled study was conducted to determine if sub-antimicrobial dose doxycycline (SDD) administered orally for 9-months as 20 mg b.i.d. resulted in an increase in doxycycline resistance or multi-antibiotic resistance of the periodontal microbiota. Seventy-Eight (78) adult periodontitis subjects were enrolled. Each subject received scaling and root planing (SRP) in the 2 qualifying quadrants and were then randomly assigned to receive either SDD or placebo treatment. Plaque samples were collected at baseline (BL), 3, 6, and 9 months, from two separate tooth sites within the SRP quadrants and from 2 sites in the non-SRP quadrants using the sterile endodontic paper point method. Tooth sites from which plaque samples were obtained must have had BL PPD of ≥ 5 to ≤ 9 mm. Plaque samples were pooled by subject as to SRP or non-SRP treatment and were plated on general purpose growth medium containing 4 μg/mL doxycycline (upper limit of "Susceptible"). The 3 most numerous colony types were individually enumerated and expressed as a percent of the total doxy-resistant bacteria cultivated. A representative of each of the 3 colony types was subcultured, identified and its MIC was determined for each of 6 antibiotics (doxycycline, minocycline, tetracycline, amoxicillin, erythromycin, and clindamycin). The results obtained for each treatment at each sample period were examined to determine if differences existed either in distribution of doxycycline-resistance or in the bacteria expressing resistance. Five taxa (*Streptococcus, Prevotella, Fusobacterium, Campylobacter, and Bacteroides*) accounted for 80% of the doxycycline-resistant isolates. These resistant isolates persisted throughout the study and were distributed similarly within each treatment group. There were no statistically (p-value < 0.05) or microbiologically significant differences between treatment groups at any post-BL visit. We conclude that a 9-month course of SDD treatment did not result in either the acquisition of doxycycline-resistance or multi-antibiotic resistance in the periodontal microbiota nor did its use result in overgrowth by doxycycline-resistant bacteria. Supported by CollaGenex Pharmaceuticals, Inc.

Effect of Sub-Antimicrobial Dose Doxycycline on Periodontal Flora. C. WALKER*, A. HEFTI, J. THOMAS, S. NANGO, J. LENNON, J. WETZEL, and C. POWALA (UF-PDRC, Gainesville, FL; WVU, Morgantown, WV; CollaGenex, Newtown, PA).

A multi-center, double-blind, placebo-controlled study was conducted to determine if sub-antimicrobial dose doxycycline (SDD) therapy, administered orally for 9-months as 20 mg b.i.d., exerted an antimicrobial effect on the subgingival microflora. Adult periodontitis subjects (n=78) with baseline probing pocket depth (PPD) ≥ 5 to ≤ 9 mm in at least 3 quadrants were enrolled. Each subject received scaling and root planing (SRP) in 2 quadrants and was randomly assigned to receive either SDD or placebo treatment. Microbial samples were collected at baseline (BL), 3, 6, and 9 months from 2 separate tooth sites within the SRP quadrants and from 2 sites in the non-SRP quadrants. Each sample site was required to have a BL PPD of ≥ 5 to ≤ 9 mm. The samples were pooled per subject by SRP or non-SRP treatment, examined by darkfield microscopy, and enumerated on selective and non-selective media. Significant reductions ($p<0.05$) were detected in the proportions of spirochetes present in the SRP/SDD-treated subjects at 3, 6, and 9 months and in the non-SRP/SDD group at month 9 compared with placebo. Analyses of the clinical indices for the sample sites revealed a mean attachment level (AttL) gain of 1.4 mm, a PPD decrease of 1.6 mm and a 22-39% decrease in BOP in the SRP/SDD subjects compared with values of 0.9 mm, 1.1 mm, and 2-16%, respectively for the SRP/placebo subjects. No significant differences ($p \leq 0.05$) were detected between SDD and placebo groups in total cultivable anaerobic flora, in the recovery of periodontal pathogens, or in the recovery of opportunistic pathogens including *Candida*. Since there were no significant differences in other bacterial groups with sensitivities similar to the spirochetes and since the latter are often associated with gingival inflammation, it was hypothesized that the reduction in spirochetes was a result of improvements in the periodontal pockets rather than a direct antimicrobial effect. We conclude that the long-term administration of SDD had no detrimental effect on the periodontal flora and did not result in either an antibiotic-induced shift in its composition or its overgrowth by periodontal and/or opportunistic pathogens. Supported by CollaGenex Pharmaceuticals, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-744

SEP 30 1998

CollaGenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your new drug application (NDA) dated August 30, 1996, received August 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Periostat™ (doxycycline hyclate USP) Capsules, 20 mg. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated August 28, October 1, November 13, December 8, 1997; January 6, 14, and 19, February 10, March 2, 18, and 31, April 23 and 28, July 9 and 29, and September 3, 14, 16, 22, 24 (2), and 25, 1998. Your submission of March 31, 1998 constituted a full response to our August 27, 1997, action letter. The user fee goal date for this application is October 1, 1998.

This new drug application provides for the use of Periostat™ (doxycycline hyclate USP) Capsules, 20 mg as an adjunct to subgingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. We acknowledge your commitment made in the teleconference with this Division on September 16, 1998, to revise the carton and container labeling so that the prominence of the established name and tradename is commensurate and in accordance with 21 CFR 201.10(g)(2).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 50-744". Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments agreed to in your submissions dated August 3, 1998, and September 14, 1998. These commitments, respectively, are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each clinical study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Roy Blay, Ph.D., Project Manager, at (301) 827-2020.

Sincerely,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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November 18, 2002

Elizabeth H. Dickinson, Esq.
Associate General Counsel
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: CollaGenex Exclusivity for PerioStat®

Dear Ms. Dickinson:

On Friday, I promised to provide the attached previous correspondence with FDA on the PerioStat® exclusivity question. I've also attached the approval letter, which says that the application is subject to the antibiotic transition provision of FDAMA.

There are some other points that would come up in a litigation that were not raised in the letter to Dr. Lumpkin, although at least some were discussed in a subsequent telephone conversation. We'll plan to discuss on Wednesday these additional points as well as the ones in the letter to Dr. Lumpkin.

We're looking forward to seeing you on Wednesday.

Sincerely,

Kate

Kate C. Beardsley

a regulation, after notice and comment, finding that the article would be lawful under this Act.

cept for purposes of section 201(g), a dietary supplement shall be emed to be a food within the meaning of this Act.

(gg) The term "processed food" means any food other than a w agricultural commodity and includes any raw agricultural com-)dity that has been subject to processing, such as canning, cook-g, freezing, dehydration, or milling.

(hh) The term "Administrator" means the Administrator of the ıited States Environmental Protection Agency.

(ii) The term "compounded positron emission tomography ug"—

(1) means a drug that—

(A) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and

(B) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (A), and is compounded in accordance with that State's law, for a patient or for research, teaching, or quality control; and

(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be ·sed in the preparation of such a drug.

) The term "antibiotic drug" means any drug (except drugs use in animals other than humans) composed wholly or partly any kind of penicillin, streptomycin, chlortetracycline, chlorphenicol, bacitracin, or any other drug intended for human use ıtaining any quantity of any chemical substance which is pro-:ed by a micro-organism and which has the capacity to inhibit destroy micro-organisms in dilute solution (including a chemily synthesized equivalent of any such substance) or any deriva-: thereof.

CHAPTER III—PROHIBITED A

PROHIBITED A

SEC. 301. [21 U.S.C. 331] The fol thereof are hereby prohibited:

(a) The introduction or delivery fo commerce of any food, drug, device, or or misbranded.

(b) The adulteration or misbrandi or cosmetic in interstate commerce.

(c) The receipt in interstate comme or cosmetic that is adulterated or misl proffered delivery thereof for pay or otl

(d) The introduction or delivery fo commerce of any article in violation of

(e) The refusal to permit access to required by section 412, 504, or 703; maintain any record, or make any re 412, 504, 505 (i) or (k), 512(a)(4)(C), 51 or the refusal to permit access to or v such required record.

(f) The refusal to permit entry or section 704.

(g) The manufacture within any Te vice, or cosmetic that is adulterated or

(h) The giving of a guaranty or un tion 303(c)(2), which guaranty or unde person who relied upon a guaranty or fect signed by, and containing the nam residing in the United States from wh the food, drug, device, or cosmetic; or undertaking referred to in section 3 undertaking is false.

(i)(1) Forging, counterfeiting, s resenting, or without proper authority label, or other identification device aut lations promulgated under the provisio

(2) Making, selling, disposing of, o trol, or custody, or concealing any pun thing designed to print, imprint, or rep name, or other identifying mark, imp any likeness of any of the foregoing u labeling thereof so as to render such dr

(3) The doing of any act which ca feit drug, or the sale or dispensing, o pensing, of a counterfeit drug.